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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,721	10/26/2001	Naohiro Terada	5853-207	9675

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EXAMINER	
KELLY, ROBERT M	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 06/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/045,721	TERADA ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8 and 10-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8 and 10-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/18/05 has been entered.

Claims 1, 8, 14, 16-17, and 20 are amended.

Claim 9 has been cancelled.

Claims 1-6, 8, and 10-20 are pending and considered.

Note re Compliance with Amendment Practice under 37 CFR 1.121(c)

It is noted that Applicant has identified claims with the term "Previously Amended". Such claim identifiers are no longer considered proper, according to current amendment practice under 37 CFR 1.121(c). However, such amendment has been entered, and will be considered. Applicant is forewarned that future amendments may be responded to with a non-responsive amendment notice. To help Applicant, the following are the allowable claim identifiers: Original; Currently Amended; Canceled; Withdrawn; Previously Presented; New; Not entered; and Withdrawn – Currently Amended.

Rejections of Canceled Claims

In light of Applicant's cancellation of claim 9, all rejections and objections to such claim are rendered moot, and thus, are withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 8, and 10-20 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 has been amended to recite the term "naïve embryonic stem cell", while not similarly amending the subsequent recitations of "stem cell" and "stem cells" in the claims. Due to this amendment, it is not clear whether these later recitations of stem cells actually refers to the naïve embryonic stem cells or to other cells, and the step of providing does not necessarily correlate with the method preamble due to such lack of clarity. Hence, the claim is rejected for lack of antecedent basis.

Claims 2-6, 8, 10 also recite the limitation "stem cell" or "stem cells", and as such these claims are also rejected for lack of proper antecedent basis, as the Examiner cannot determine which of the cells Applicant is referring to.

Claims 10-12 are rejected because they limit the time frame of step E of claim 1 to ranges outside the range claimed in claim 1. Given the prosecution history, and Applicant's present

amendments, it is unclear whether such limitations applied to the original claim only, or are meant to apply to step E of the presently-claimed embodiment of claim 1.

Claims 2-6, 8, and 10-20 are also rejected for depending from rejected base claims and not overcoming the lack of clarity in such base claims.

Claim Rejections - 35 USC § 112

Claims 1-6, 8, and 10-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is made on the basis of the limitations newly added to the base claims: (i) "naïve embryonic stem cells"; (ii) "culturing the stem cells for at least about 3 days in the absence of a test substance"; and (iii) "culturing for at least about 14 days, the first and second subcultures respectively".

Applicant's claims now embrace the term "naïve embryonic stem cells". Applicant has not provided any location within the originally filed specification and claims where such support is found. Moreover, the Examiner has carefully reviewed the specification and found no such implicit or explicit support for naïve embryonic stem cells. Moreover, such embryonic stem cells may be naïve because they are not transformed with any nucleic acids, because they are capable of differentiation into any cell of the organism, or because they were immediately isolated from nature, among other things. However, dependent claim 5 is to a cell line, which Applicant argues is not naïve embryonic stem cell (Applicant's argument of 4/18/05, p. 8,

paragraph 1). Therefore, this limitation subject to a new matter rejection; however, for purposes of compact prosecution, this claim limitation will be read to encompass any embryonic stem cell.

Applicant's claims now embrace the term "culturing the stem cells for at least about 3 days in the absence of a test substance", which occurs before addition of test substance. Applicant has not provided any location within the originally filed specification and claims where such support is found. Moreover, the Examiner has only found one recitation of culturing the cells for three days, and that is after differentiation of cells (EXAMPLE 2). Furthermore, there is no reason that the Examiner can determine for such specific time frames of pre-culturing. Hence, the Examiner is unable to determine that Applicant had possession of the presently claimed invention at the time of filing. Therefore, this limitation is subject to a new matter rejection.

Applicant's claims now embrace the term, "culturing for at least about 14 days, the first and second subcultures respectively, [after addition of the test substance]". Applicant has not provided any location within the originally filed specification and claims where such support is found. Moreover, the Examiner's review of the specification and claims has only found support for 7-14 days, less than 8-10 days, and less than 15-18 days (pp. 9-10, paragraph bridging) as well as 3 days (EXAMPLE 2). These recitations do not provide the requisite support for the limitation "at least about 14 days" in the claims. If Applicant wishes to rely on the statement, "This time period may vary depending on the particular type of stem cells used and the particular differentiation pathway being analyzed." (p. 9, last paragraph), Applicant should bring the whole statement into the claims, as the limitation to at least about 14 days would indicate that a particular genera of stem cell and differentiation path are involved, given the Examiner's

understanding of the paragraph bridging pp. 9-10 of the specification. Hence, the Examiner is unable to determine that the Applicant had possession of the presently claimed invention at the time of filing. Therefore, this limitation is subject to a new matter rejection.

Claim Rejections - 35 USC § 103 – Old Rejections

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

In light of the amendments, the rejections of Claims 1 and 14-19 under 35 U.S.C. 103(a) as being unpatentable over WIPO document No. WO 99/10535 to Liu, filed 21 August 1997, published 4 March 1999, for reasons of record in the Official Actions of 10 September 2003 and 8 April 2004, are withdrawn.

In light of the amendments, the rejections of Claims 1, 8, and 10-13 under 35 U.S.C. 103(a) as being unpatentable over WIPO document No. WO 99/10535 to Liu, filed 21 August 1997, published 4 March 1999, as applied to claim 1 above, and further in view of U.S. Patent No. 5,328,844 to Moore, filed 24 June 1992, patented 12 July 1994, for reasons of record in the Official Actions of 8 April 2004 and 10 September 2003, are withdrawn.

In light of the amendments, the rejections of Claims 1and 6 under 35 U.S.C. 103(a) as being unpatentable over Liu '535 as applied to claim 1 above, and further in view of Thomson, et

al. (1998) Science, 282:1145-1147, for reasons of record in the Official Actions of 8 April 2004 and 10 September 2003, are withdrawn.

In light of the amendments, the rejections of Claims 1 and 20 under 35 U.S.C. 103(a) as being unpatentable over Liu, as applied to claim 1 above, and further in view of U.S. Patent No. 5,143,854 to Pirrung, for reasons of record in the Official Actions of 8 April 2004 and 10 September 2003, are withdrawn.

In light of the amendments, the rejection of claim 5 under 35 U.S.C. 103(a) as being unpatentable over Liu and further in view of U.S. Patent No. 5,874,301 to Keller, for reasons of record in the Official Actions of 8 April 2004 and 10 September 2003, is withdrawn.

Applicant's arguments with regard to Thomson are noted, but they are mooted by the new grounds of rejection, below.

Claim Rejections – 35 USC § 103 – Liu/Keller

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 and 10-12 remain rejected, and claims 6, 8, and 14-19 under 35 U.S.C. 103(a) as being unpatentable over Liu and further in view of U.S. Patent No. 5,874,301 to Keller, for reasons of record in the Official Actions of 8 April 2004 and 10 September 2003, as well as the reasons stated below.

Claims 1 and 14-19 disclose methods to screen substances for the ability to promote cellular differentiation in embryonic stem cells in which cultured stem cells are contacted with a test substance, cultured, and tested for cellular markers of differentiation. The claims further require at least two separate cultures, cultured for at least about 3 days, then each contacted with a different substance, cultured again for at least about 14 days, and testing for increased tissue-specific gene expression as the cellular marker(s) of differentiation. The depending claims limit the method of measuring expression of genes to measuring the cellular changes in mRNA expression, wherein such measuring can include isolation of total cellular RNA, cellular mRNA, reverse transcription to obtain cDNA, PCR amplification, immobilization of mRNA, and probing for specific mRNAs.

Although Liu '535 does not define the steps contemplated by Applicant in the same manner that Applicant defines these steps, Liu '535 obviates all of the limitations of the Applicant's claims. Specifically, Liu '535 discloses "methods to identify a therapeutic agent that modulates the expression of at least one stem cell gene associated with the differentiation ... of stem cells" (Liu '535, ABSTRACT). Such stem cells include the use of embryonic stem cells, because the definition of stem cells includes totipotent cells, which are embryonic stem cells (p. 6, paragraph 3). Liu '535 teaches the identification of stem cell genes that are differentially expressed at various stages of differentiation by preparing gene expression profiles before and after differentiation (Id., p. 5, lines 1-6). This encompasses defining those genes that are expressed in a tissue-specific manner, as well as those genes that are down-regulated in a tissue-specific manner, and therefore defines the markers that would be analyzed for increased tissue-specific gene expression in step (E) of Claim 1. Furthermore, Liu '535 teaches a comparison of

the gene expression profiles with that of a stem cell population treated with a substance, to identify substances that modulate the expression of these genes, and therefore would be associated with stem cell differentiation (Id., p. 5, lines 7-18, and EXAMPLES 2 and 3). Moreover, Liu '535 obviates the limitation of culturing the cells after contacting the cells with the substance, as one of ordinary skill in the art at the time of the invention would have known that time is needed to allow differentiation of the cells and changes in gene expression to take place. Liu '535 also teaches the aspects of mRNA isolation (p. 20), total cellular RNA isolation (p. 20), reverse transcription (p. 20), PCR amplification (pp. 23-24), immobilized mRNA (EXAMPLE 4), and probing for mRNA (EXAMPLE 4).

Keller '301 teaches the isolation of embryonic cell populations (TITLE), including embryonic stem cells (e.g., col. 5, paragraphs 5-6; col. 2, lines 5-8), which may be cultured for at least about 3 days prior to differentiation (e.g., col. 7, paragraph 1), which cells may then be used in differentiation experiments to derive various differentiated cell types (EXAMPLES). One such cell type is hepatocytes, which requires culturing under appropriate conditions (i.e., differentiation conditions) for at least about 14 days (e.g., col. 20, paragraph 4). Keller '301 also teaches mouse embryonic stem cells (Example 1). Such cells may also be derived from, *inter alia*, humans (col. 6, paragraph 2). Furthermore, culturing conditions include humidified, 37 degrees C, and carbon-dioxide-containing environments (e.g., col. 10, paragraph 1; EXAMPLE 1).

In view of Liu, one of ordinary skill in the art at the time of invention by Applicant (hereinafter the "Artisan") would have been motivated to identify drug candidates for promoting tissue-specific differentiation of a stem cell as taught by Liu, by providing a number of test

substances (otherwise there would be no pool of substances from which to identify a substance that works), and culturing cells *in vitro* in the presence of each substance, individually, under conditions that allow for such differentiation, and analyzing the cells in the cultures for increased tissue-specific gene expression markers using the embryonic stem cells of Keller. The Artisan would have been motivated to do so in order to identify agents that cause the differentiation of such embryonic stem cells into, *inter alia*, leukocytes and erythrocytes. Moreover, the Artisan would have had a reasonable expectation of success, as Liu had already shown that such screens could work *in vivo*, and culture techniques for the specific cells had already been demonstrated by Keller.

Response to Arguments – Liu and Liu/Keller

Applicant's arguments of 4/18/05 have been fully considered but are not found persuasive.

Arguments re Liu

Applicant argues that Liu does not teach or suggest the limitations of culturing the embryonic stem cells for at least about 3 days prior to exposure to an agent that effects differentiation of the cells, as well as subsequent culturing for at least about 14 days (Applicant's argument of 4/18/05, pp. 5-6, paragraph bridging-p. 6, paragraph 3; p. 7, last paragraph).

Such is not persuasive. The Examiner admits that such specific time frames are not taught, but the argument is mooted in view of the new ground of rejection (ABOVE), wherein Keller teaches the specific time frames encompassed by Applicant's presently claimed methods.

Applicant argues that Keller does not teach embryonic stem cells *per se*, but cell lines, and as such, do not make up for the deficiencies of Liu, and therefore naïve embryonic stem cells are not obvious.

Such is not persuasive. First, as has been stated (ABOVE), Liu teaches totipotent cells, which are embryonic stem cells. Second, Keller may use cell lines in the experiments section, but they teach using any embryonic stem cell (e.g., cols. 5-6). Third, Applicant also uses an embryonic stem cell line, e.g., EXAMPLE 2, and such does not appear to limit their claims to naïve ES cells. Fourth, naïve cannot mean untransformed, as the R1 cells of claim 5 are transformed.

Claim Rejections – 35 USC § 103

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Liu and Keller as applied to claim 1 above, and further in view of Kondoh, et al. (May, 1999) J. Biochem. Biophys. Meth., 39: 137-142.

As shown above, Claim 1 is obviated by Liu and Keller, however, neither Liu nor Keller teach or suggest the use of the murine embryonic cell line R1.

On the other hand, such cell line was a well-known and commonly used cell in the laboratory. Kondoh teaches that such cell line may be used to reconsititute the various tissues of a mouse (e.g., ABSTRACT).

Hence, at the time of invention by Applicant, it would have been obvious to modify the methods of Liu and Keller with the R1 cell line of Kondoh. The Artisan would have been motivated to do so because it was a commonly used ES cell line, which could produce the various tissues of the mouse. Moreover, the Artisan would have had a reasonable expectation of success, as Liu and Keller had shown the techniques possible with mouse ES cells, and Kondoh demonstrated that R1 stem cells could undergo similar differentiations.

Claim Rejections – 35 USC § 103

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Liu and Keller as applied to claim 1 above, and further in view of U.S. Patent No. 5,328,844 to Moore, filed 24 June 1992, patented 12 July 1994.

As shown above, Claim 1 is obviated by Liu and Keller, however, neither Liu nor Keller teach or suggest the use of microtiter plates.

On the other hand, Moore teaches culture media useful for establishing growing and maintaining mammalian cells in culture (ABSTRACT). More also teaches that cells are cultured in, *inter alia*, multi-well plates (microtiter plates) (EXAMPLE 2).

Hence, at the time of invention by Applicant, it would have been obvious to modify the methods of Liu and Keller with the microtiter plates of Moore. The Artisan would have been motivated to do so because such plates are useful for growing and maintaining cells. Moreover, the Artisan would have had a reasonable expectation of success because Moore had shown that cells could be cultured in these plates successfully.

Response to Argument – Liu/Moore

Applicant's argument of 4/18/05 has been fully considered but such is not found persuasive.

Applicant's argue that Moore does not rectify the fact that Liu does not specifically teach the aspects of humidified, carbon-dioxide-containing, 37 degree F culturing (Applicant's argument of 4/18/05, p. 6, paragraph 4-p. 5, paragraph 2).

Such is not found persuasive in light of the new ground of rejection, wherein it is taught by Keller to culture the cells in such claimed conditions (ABOVE).

Claim Rejections – 35 USC § 103

Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Liu and Keller as applied to claim 1 above, and further in view of U.S. Patent No. 5,143,854 to Pirrung.

As shown above, Claim 1 is obviated by Liu and Keller, however, neither Liu nor Keller teach or suggest the use of gene chip technology.

On the other hand, Pirrung '854 teaches the use of such gene chip technology for the analysis of arrays of peptides for activity (ABSTRACT). Specifically, Pirrung '854 teaches that such technology is useful for, e.g., "[s]creening large numbers of polymers for biological activity," (e.g., col. 3, lines 39-41).

Moreover, one of ordinary skill in the art at the time of the invention it was obvious to modify the teachings of Liu and Keller by the gene chip technology of Pirrung '854. One would have been motivated to do so because Pirrung allows for the controlled synthesis of a variety of polymers in a small space, which is particularly suited to the screening system described

(Pirrung, ABSTRACT). Also, because both Liu '535 and Pirrung '854 have been shown successful, absent reason to believe otherwise, one would have expected success with their combination.

Response to Argument – Liu/Keller and Pirrung

Applicant's argument of 4/18/05 has been fully considered but is not found persuasive.

Applicant argues that Pirrung is limited to polypeptides and their binding sites (Applicant's argument of 4/18/05, p. 9, paragraphs 4-5).

Such is not persuasive. Pirrung specifically states polymers (See Official Action of 11/15/04, p. 12, paragraph 3) and Applicant's claims are not limited to non-polypeptides or non-polymers (Id.).

Applicant argues that Pirrung is limited to screening of polypeptides and their binding sites, and does not teach or suggest the use of such technology for the determination of expression levels of mRNA in such methods as claimed. Applicant further argues that the Artisan would not recognize, given the disclosures of Liu and Pirrung, how to culture the cells, under what conditions, give the gene chip technology (Applicant's argument of 4/18/05, p. 9, paragraph 5).

Such is not persuasive. First, the conditions of culturing are unaltered by Pirrung. Pirrung is used for the determination of the **binding** of mRNA to **nucleic acid polymers**. The production of such polymers is known in the art, otherwise the other RNA binding assays could not be carried out. Also, the binding of one RNA to another is known in the art, and is recognized by the Artisan as a binding with similar effects using gene chip technology as that

given for even polypeptide bindings. As evidence of this, the Examiner supplies the following quotation from Pirrung:

> Certain macromolecules are known to interact and bind other molecules having a very specific three-dimensional spatial and electronic distribution. Any large molecule having such specificity can be considered a receptor, whether it is an enzyme catalyzing hydrolysis of a metabolic intermediate, a cell-surface protein mediating membrane transport of ions, a glycoprotein serving to identify a particular cell to its neighbors, an IgG-class antibody circulating in the plasma, an oligonucleotide sequence of DNA in the nucleus, or the like. The various molecules which receptors selectively bind are known as ligands.

Pirrung, col. 1, paragraph 6.

As such, Pirrung recognizes that RNA binding to RNA or DNA has such three-dimensional spatial and electronic distribution (it is noted that Pirrung also notes DNA as one such molecule). Moreover, the binding of nucleic acids to via base-pair binding was first discovered by the well-known experiments of Watson and Crick in the 1950s. Hence, it is obvious to use this technique to identify such binding.

Applicant argues that due to the age of Pirrung, seven years before the filing date of Liu would have made their combination non-obvious, and is not even obvious to Liu (Applicant's argument of 4/18/05, p. 9, paragraph 5).

Such is not persuasive. First, whether Liu did or did not think the use of gene chip technology was obvious is not the question: Liu did not address it, but that means nothing; and the actual question is whether the Artisan thought it obvious, not Liu.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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